REMARKS

The Claim Amendments

Claims 1 and 3 have been amended such that the term "pharmaceutically acceptable derivative" has been replaced with the term "pharmaceutically acceptable salt." Support for this amendment is found on page 51, lines 23-24, of the specification.

Claim 1 has been amended such the alternative embodiment of y being zero has been deleted. Support for this amendment is found in the claim as originally filed and in the corresponding specification text. Since y is one in the amended claim, R^1 cannot be hydrogen. Therefore, the proviso has been deleted, because it no longer applies. Furthermore, in claim 1 the alternative embodiment that recites "two R^4" groups adjacent to each other on the phenyl ring has been deleted.

Claims 2, 6-25, and 30 have been canceled.

Claim 26 has been amended to recite a composition comprising a compound of formula **I**. Support for this amendment is found on page 50, lines 16-20, of the specification.

Claims 27 and 32 have been amended to recite additional therapeutic agents useful in the compositions or methods of the claims. Support for these amendments is found on page 57, line 1, to page 58, line 2, of the specification

Claim 28 has been amended by adding the term "*in vitro*" to further define the term "biological sample" in the claim. Support for this amendment is found in on page 58, lines 17-21, of the specification, wherein *in vitro* uses of the compounds of the invention are described.

Claim 29 has been amended to recite a method of treating or lessening the severity of various specific Src-mediated diseases or conditions in a patient. Support for this amendment is found in original claim 30.

Claim 31 has been amended to recite a method of treating or lessening the severity of various specific Lck-mediated diseases or conditions in a patient. Support for this amendment is found in original claims 29 and 31.

Claims 33 and 34 have been amended to recite a composition for coating a prosthesis, artificial valve, vascular graft, stent, or catheter and said medical devices comprising the composition, respectively. Support for these amendments is found on page 60, lines 5-29.

The Response

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1-34 under 35 U.S.C. § 112, first paragraph, and alleges that the specification, while being enabling for compounds of formula **I** or a pharmaceutically acceptable salt thereof, does not provide enablement for pharmaceutically acceptable derivatives. Claims 1 and 3 have been amended to recite compounds of formula **I**, or salts thereof, thus obviating the rejection.

The Examiner has rejected claims 26-34 under 35 U.S.C. § 112, first paragraph, and alleges that: (i) the specification, while being enabling for a pharmaceutical composition, does not reasonably provide enablement for a composition to detectably inhibit Src or Lck protein kinase activity; (ii) the specification does not reasonably provide enablement for inhibiting Src or Lck kinase activity in a biological sample, wherein said biological sample encompasses animals and human beings; (iii) the specification, while being enabling for the treatment of rheumatoid arthritis, does not enable a method of treating or lessening the severity of all other diseases or conditions mediated by Src or Lck kinases; and (iv) the specification does not provide an enabling disclosure for the type of therapeutic applications of the devices of the invention. Further, the Examiner alleges that in view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Regarding item (i), claim 26 has been amended to recite a pharmaceutical composition comprising a compound of formula **I**, thus obviating the rejection.

Regarding item (ii), one of skill in the art would recognize that inhibiting Src or Lck activity in a biological sample does not encompass administration to an animal. Similarly, one skilled in the art would recognize that claim 28 is not a "reach-through" claim, as alleged by the Examiner, because the claim does not relate to methods of treating diseases, disorders, or conditions. However, in order to expedite prosecution, claim 28 has been amended such that it

recites a method of inhibiting Src or Lck activity in a biological sample *in vitro*. One skilled in the art, applying the general knowledge of the art in conjunction with the teachings of the specification, would clearly be able to practice the invention. See, for example, Examples 11 and 12 on pages 69-74 of the specification, which describe the *in vitro* activity of compounds of the invention against Src or Lck kinase.

Regarding item (iii), applicants traverse. Claims 29 and 31 have been amended to recite methods of treating specific diseases or disorders with the compounds or compositions of the invention. These diseases and disorders include bone disorders, such as osteoporosis, bone metastasis, and Paget's disease; proliferative diseases, such as colon cancer, breast cancer, hepatic cancer, pancreatic cancer, B-cell leukemia, lymphoma, or leukemia; and T-cell-mediated disorders such as autoimmune disease, inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, psoriasis, lupus, graft vs. host disease, T-cell mediated hypersensitivity disease, Hashimoto's thyroiditis, Guillain-Barre syndrome, chronic obstructive pulmonary disorder, ischemic or reperfusion injury, atopic dermatitis, contact dermatitis, asthma, or allergies.

The nexus between inhibition of Src or Lck and the treatment of T-cell mediated diseases was well established at the time of the invention. As indicated in the specification on page 3, lines 29-33, Lck plays a role in T-cell signaling. Mice that lack the Lck gene have a poor ability to develop thymocytes. See abstract of Molina et al., *Nature*, 357:161-164, 1992, (hereafter, "Exhibit A"). Further, Lck inhibitors have T-cell modulating activity in an *in vivo* murine model that measured IL-2 production. See the subsection titled "In Vivo Activity" on page 1343 of Goldberg et al., *J. Med. Chem.* 46(8):1337-1349, 2003 (hereafter, "Exhibit B"). In another example, a Lck inhibitor was reported to have significant inhibitory activity in murine models of T-cell- and monocyte-mediated responses when administered topically, subcutaneously, or orally. See the description of BMS-279700 in the left hand column on page 1216 of Kamens et al., "Lck inhibitors as a therapeutic approach to autoimmune disease and transplant rejections," *Curr. Opin. Invest. Drugs* 2(9):1213-1219, 2001 (hereafter, "Exhibit C"). Thus, the teachings of the specification, combined with the state of the art at the time the invention was made, clearly

enable a method of treating T-cell mediated diseases with the Src/Lck inhibitors of the instant invention.

Similarly, the nexus between inhibition of Src or Lck and the treatment of proliferative diseases was also established at the time of the invention, as discussed on page 3, lines 13-25, of the specification. It has been observed that the expression of Src was elevated in the tumorous and non-tumorous portion of hepatocellular carcinoma tissue but not in normal tissue. See the abstract of Maski et al., *Hepatology* 27:1257-1264, 1998 (hereafter, "Exhibit F"). Further, inhibition of Src or Lck blocks proliferation of a variety of different cancer cell types or tissues, For example, the lack of Src expression in a double negative mutant mammary carcinoma cell line strongly blocked hepatocyte growth factor-induced motility and colony growth. See the abstract of et al., *Cancer Res.* 59:6145-6152, 1999 (hereafter, "Exhibit D"). In addition, the Src-specific inhibitor herbimycin A decreased cell growth in pancreatic cancer cells. See page 505 of Lutz et al., *Biochem. Biophys. Res. Comm.* 243:503-508, 1998 (hereafter, "Exhibit E"). Antisense Src expressed in ovarian and colon tumor cells has also been shown to inhibit tumor growth. See the abstracts of Wiener et al., *Clin. Cancer Res.*, 5:2164-2170, 1999 (hereafter, "Exhibit G") and Staley et al., *Cell Growth Diff.*, 8:269-274, 1997 (hereafter, "Exhibit H"). Further, Lck-specific antisense oligonucleotides blocked Lck induction and prevented subsequent B cell activation and immortalization. See the right hand column of page 8669 of Cheung et al., *J. Biol. Chem.* 266:8667-8670, 1991 (hereafter, "Exhibit I"). Thus, the ample teachings in the art that inhibiting Src and/or Lck can inhibit proliferation of a wide variety of different cancer cells or tissues, combined with the teachings of the specification, fully enable the claimed invention with respect to proliferative disorders.

The use of Src inhibitors in the treatment of animal models of bone disorders was also established at the time of the invention. For example, in an osteoporosis model, it was known that Src inhibitor CGP77675 partially reversed the deterioration of bone architecture and loss of bone mass in ovariectomized rats. See Figure 2 and right hand column on page 494 of Susa et al., "Src inhibitors: drugs for the treatment of osteoporosis, cancer or both?," *Trends in Pharm. Sci.*, 21:489-495, 2000 (hereafter, "Exhibit J"). Further, breast cancer cells with elevated Src expression (MDAsrc527 cells) developed increased size of osteolytic bone metastases compared

with cells in which Src activity had been abolished (MDAsrc295 cells) in a murine model of metastatic bone disease. See Results section from pages 5029 to 5030 in Myoui et al., Cancer Research 63:5028-5033, 2003 (hereafter, "Exhibit K"). Thus, the teachings of the specification, taken together with the state of the art, provide enablement for a method of treating osteoporosis and other bone disorders.

Taken together with the specification, Exhibits A, B, C, D, E, F, G, H, I, and K show that there is a reasonable correlation between the Src/Lck inhibitors of the invention, the data showing their Src or Lck inhibitory activity, and the use of these compounds to treat the diseases recited in amended claims 29 and 31 or the compositions and devices recited in claims 33 and 34, respectively.

Regarding item (iv), applicants have amended the claims to recite compositions for specific devices whose operation would be compromised by vascular remodeling, thus obviating the rejection. Applicants note that an association between agonist-induced Src activation and chemotaxis of vascular smooth muscle cells was known at the time of the invention and it was demonstrated that an antibody that inhibits Src dramatically inhibited the migration of individual smooth muscle cells. See the abstract of Mureebe et al., *Surgery* 122(2):138-144, 1997 (hereafter, "Exhibit L"). Further, Exhibit L states that Src inhibitors would be useful in controlling intimal hyperplasia. Thus, claims 33 and 34 are fully enabled given the teachings of the specification and the state of the art at the time the invention was made.

Regarding the Examiner's objection that the specification allegedly fails to guide or enable the skilled artisan to practice the invention without undue experimentation, the term "undue experimentation" applies to that requiring ingenuity beyond that expected of one of ordinary skill in the art. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine" (MPEP 2164.06). In each case, the indicated treatment is enabled in the specification and methods of administering the compounds of the invention are taught (see pages 52-56 of the specification). A skilled artisan would be able to discern an appropriate dosage and method of use based upon the information provided in the specification along with the general knowledge of one skilled in the art. Thus, the claimed invention is enabled by the specification as originally filed. For the reasons presented above,

applicants therefore respectfully request that the Examiner withdraw his rejection of the instant claims under 35 U.S.C. § 112.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 1-34 under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter regarded as the invention of the instant application. In particular, the Examiner asserts the following: (i) the recitation of the phrase "pharmaceutically acceptable derivative" is open ended; (ii) there is insufficient antecedent basis for the limitation of two R^4 substituents in claim 1; and (iii) no therapeutic agents are recited in claims 27 and 32.

Regarding item (i), the word "derivative" has been replaced with the word "salt" in claims 1 and 3, thus obviating the objection. Regarding item (ii), the alternative embodiment in claim 1 of a phenyl ring comprising two R^4 substituents has been deleted, thus obviating the objection. Regarding item (iii), claims 27 and 32 have been amended to recite specific therapeutic agents, thus obviating the rejection.

Rejection under 35 U.S.C. § 102(b)

The Examiner has rejected claims 1-3, 5, 8, and 26-34 under 35 U.S.C. § 102(b) as allegedly being anticipated by Green et al., International Patent Application Publication No. (WO 01/12621 A2), hereafter "Green." Applicants note that Green is not a proper reference for a 102(b) rejection. The publication date of Green is February 22, 2001. The instant application claims priority to U.S. Provisional Patent Application 60/302,969, filed July 3, 2001, which is less than one year after the publication date of Green. Further, claim 1 has been amended such that y is one. Thus, R^1 is cannot be hydrogen, as is the case for the compounds of Green. Applicants therefore respectfully request that the Examiner withdraw his rejection of the instant claims under 35 U.S.C. § 102(b).

Rejection under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-34 under 35 U.S.C. § 103(a) as allegedly being obvious over Green. The Examiner asserts that it would have been obvious to select any of the species of the genus taught by Green, including those compounds recited in the instant claims, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole. Applicants traverse.

As discussed above, amended claim 1 is novel over Green. Further, Green does not teach nor suggest compounds having a substituent at the 5-position of the pyrimidine ring (i.e., the R^1 group of formula **I** as recited in claim 1). Thus, claims 1-34 are not obvious in light of Green.

Rejection under obviousness-type double patenting

The Examiner has rejected claims 1-33 under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-11 of U.S. Patent No. 6,693,108 (hereinafter "the '108 patent"). The Examiner has also rejected claims 1-17 under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-17 of U.S. Patent No. 6,689,778 (hereinafter "the '778 patent"). The Examiner asserts that the claims of the instant application are not patentably distinct from the claims of the '108 patent or the '778 patent because the instant claims substantially overlap the reference claims. Applicants traverse in part.

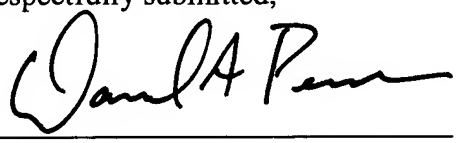
The amended claims recite compounds of formula **I**, wherein R^1 is not a hydrogen, whereas analogous claims of the '108 patent recite compounds in which the substituent corresponding to R^1 is a hydrogen. As argued above in the context of the 35 U.S.C. § 103(a) rejection, compounds of formula **I** in which R^1 is not hydrogen are patentably distinct from compounds of formula **I** wherein R^1 is hydrogen. Applicants therefore respectfully request that the Examiner withdraw his obviousness-type double patenting rejection of the instant claims over the '108 patent.

As for the obviousness-type double patenting rejection over the '778 patent, applicants stand ready to provide a terminal disclaimer over the '778 patent upon indication of allowable subject matter.

Conclusion

Applicants request that the Examiner enter the claim amendments, consider the matters discussed above, rejoin the withdrawn claims, and allow the amended and rejoined claims to pass to issue. Should the Examiner deem expedient a telephone discussion to further the prosecution of the above application, applicants request that the Examiner contact the undersigned.

Respectfully submitted,



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